Updates in Diffuse Large B-cell Lymphoma

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Disclosure of Conflicts of Interest

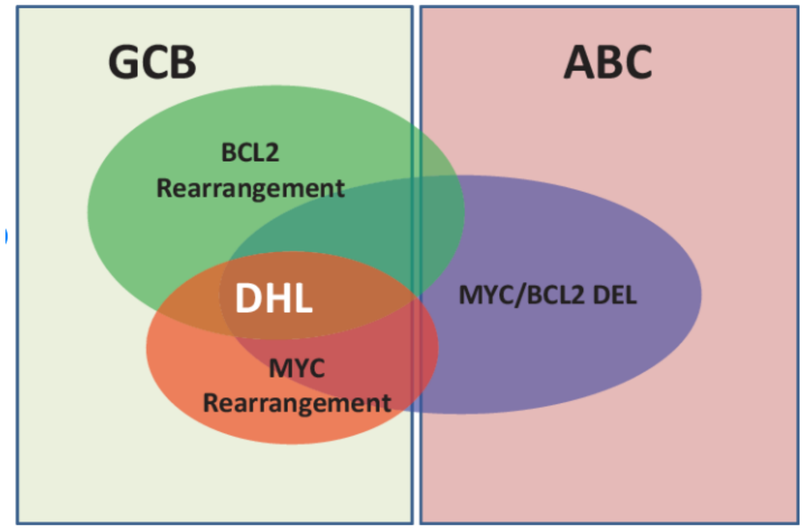
Brian Hess, MD, has the following financial relationships to disclose:

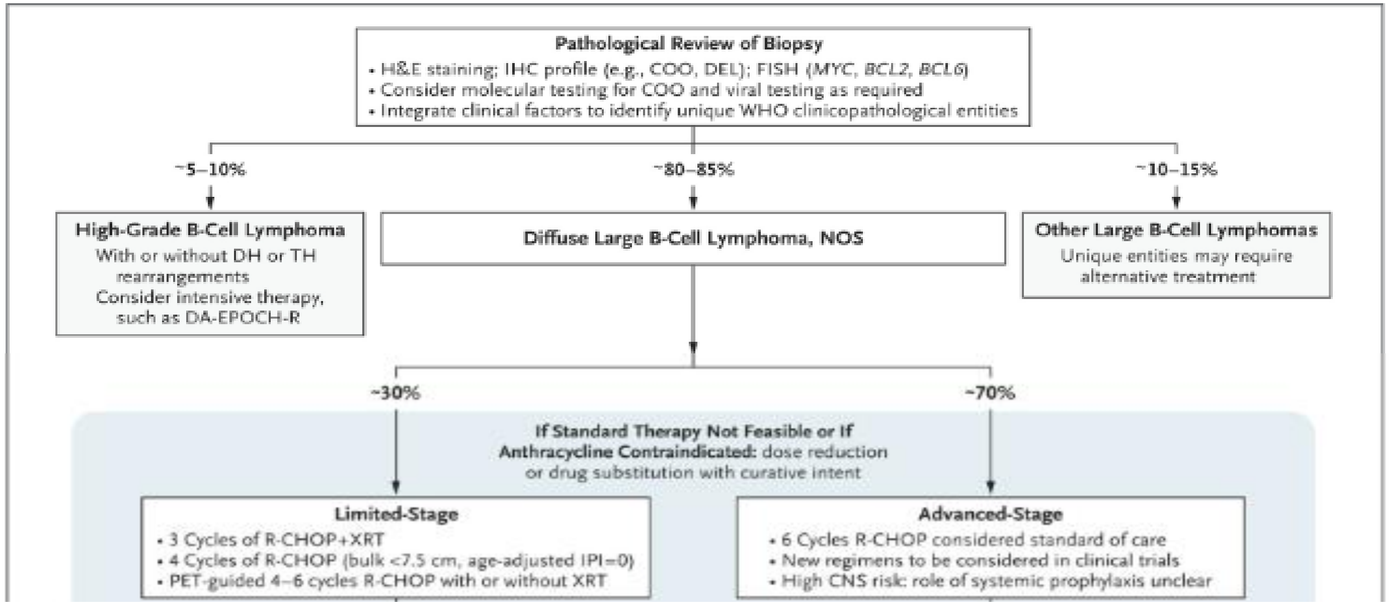
- Consultant: ADC Therapeutics
- Speaker: BMS

Agenda

- Update of frontline trials in DLBCL
- Treatment options in relapsed Large Cell Lymphoma (with an emphasis on CAR-T)
- On the horizon for DLBCL

DLBCL Classification





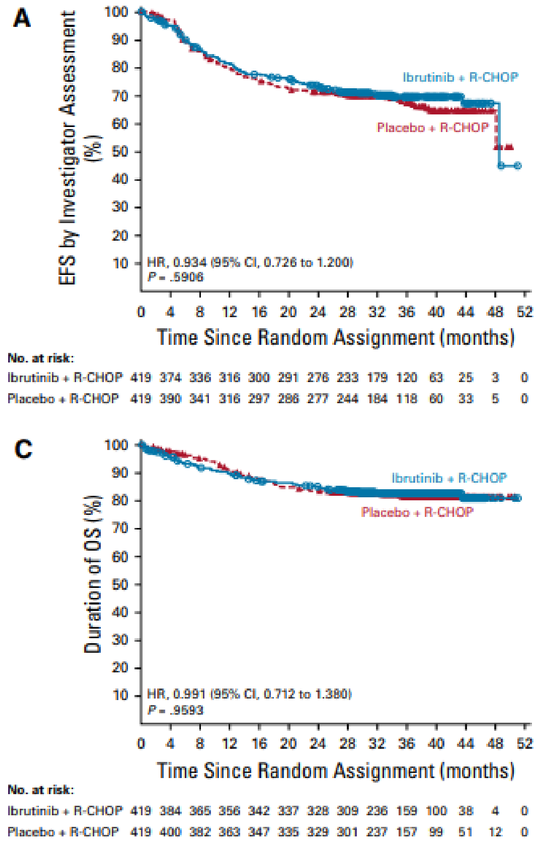
Sehn LH, Salles G. N Engl J Med. 2021 Mar 4;384(9):842-858.
Li, Shaoying & Lin, (2018). Expert Review of Hematology. 11. 1-12.

Overcoming Limitations with R-CHOP in DLBCL

- R-CHOP vs R-CHOP + Lenalidomide → did not meet primary PFS endpoint
- R-CHOP vs R-CHOP + Bortezomib → did not meet primary PFS endpoint
- R-CHOP vs DA-EPOCH-R → increased toxicity and no improvement in PFS or OS for DA-EPOCH-R (15.6% with DE and 5.2% with double hit)
- R-CHOP vs O-CHOP → no benefit with replacing rituximab with obinutuzumab
- R-CHOP vs R-CHOP + Ibrutinib → ?
- R-CHOP vs R-CHP + Polatuzumab vedotin → R-CHP + Pola 'wins'

Nowakowski GS, et al. J Clin Oncol. 2021 Apr 20;39(12):1317-1328
Davies A, et al. Lancet Oncoogy. 2019 May;20(5):649-662
Bartlett NL, et al. J Clin Oncol. 2019 Jul 20;37(21):1790
Sehn LH, et al. J Hematol Oncol. 2020 Jun 6;13(1):71
Younes A, et al. J Clin Oncol. 2019 May 20;37(15):1285-1295.
Tilly H, et al. N Engl J Med. 2022 Jan 27;386(4):351-363.

PHOENIX: R-CHOP vs R-CHOP + Ibrutinib



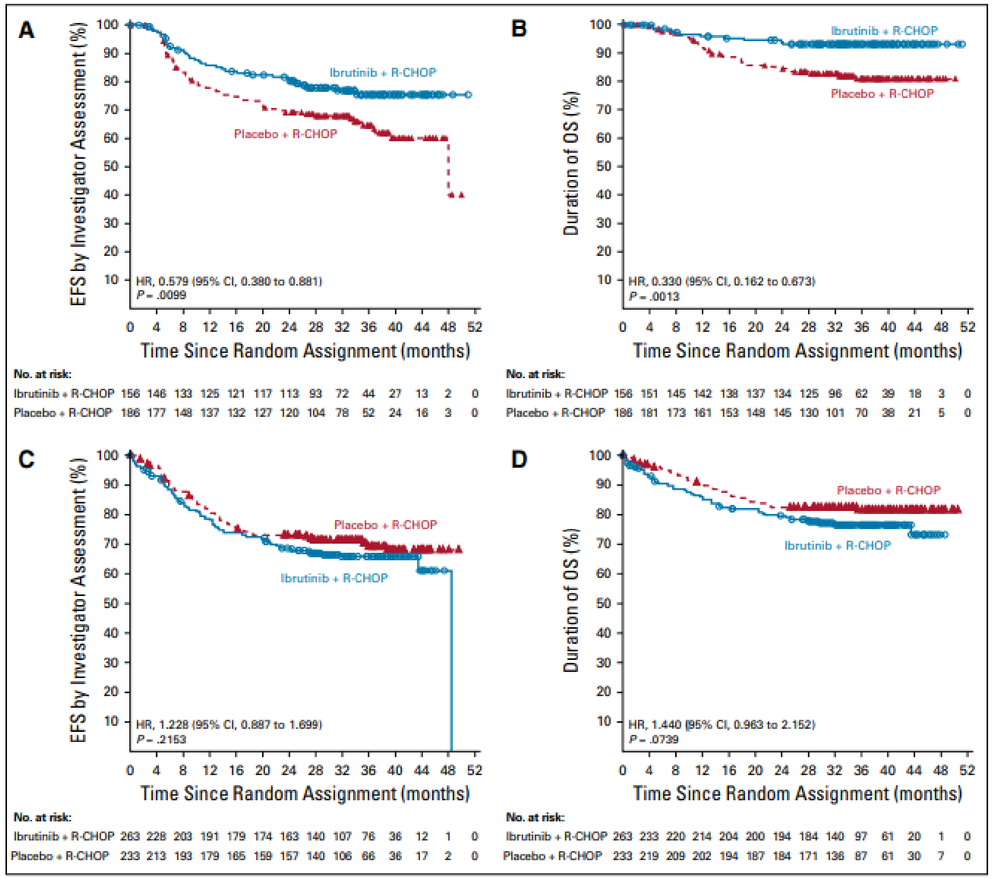


FIG 4. Kaplan-Meier survival curves for event-free survival (EFS) and overall survival (OS) by cutoff of age 60 years in the intent-to-treat population. (A) EFS, age younger than 60 years (n = 342). (B) OS, age younger than 60 years (n = 342). (C) EFS, age 60 years or older (n = 496). (D) OS, age 60 years or older (n = 496). HR, hazard ratio; R-CHOP, rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone.

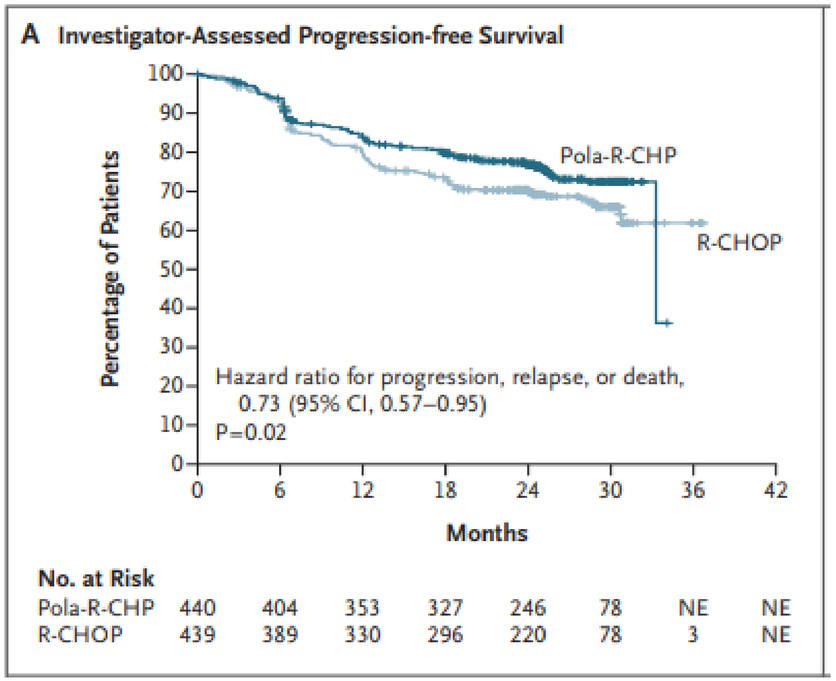
Younes A, et al. J Clin Oncol. 2019 May 20;37(15):1285-1295. doi: 10.1200/JCO.18.02403. Epub 2019 Mar 22. PMID: 30901302; PMCID: PMC6553835.

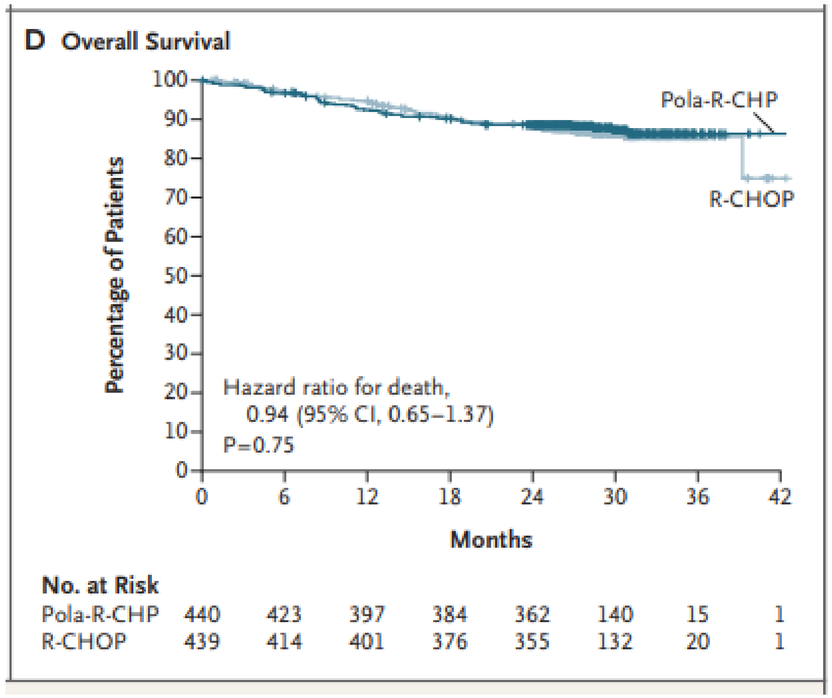
Wilson WH, et al. Cancer Cell. 2021 Dec 13;39(12):1643-1653.e3. doi: 10.1016/j.ccell.2021.10.006. Epub 2021 Nov 4. PMID: 34739844; PMCID: PMC8722194.

POLARIX: R-CHOP vs R-CHP+Pola PFS

Inclusion:

- IPI 2-5 (3-5 → 62%)
- 18-80 years old





- 2 year PFS 76.7% vs 70.2%
- NNT: ~ 15

Tilly H, et al. N Engl J Med. 2022 Jan 27;386(4):351-363.

POLARIX: R-CHOP vs R-CHP+Pola Safety

Table 3. Adverse Events during the Treatment Period (Safety Population).*

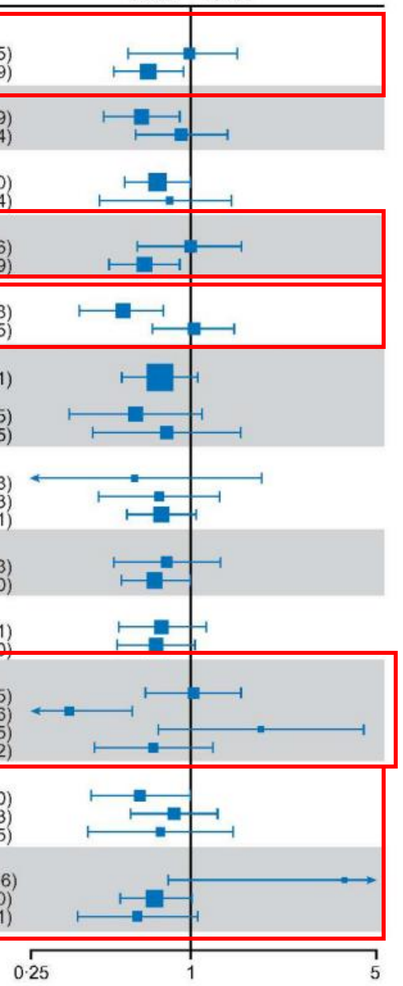
Adverse Event	Pola-R-CHP (N=435)		R-CHOP (N=438)	
	Any Grade	Grade 3 or 4	Any Grade	Grade 3 or 4
	number of patients (percent)			
Peripheral neuropathy†	230 (52.9)	7 (1.6)	236 (53.9)	5 (1.1)
Nausea	181 (41.6)	5 (1.1)	161 (36.8)	2 (0.5)
Neutropenia	134 (30.8)	123 (28.3)	143 (32.6)	135 (30.8)
Diarrhea	134 (30.8)	17 (3.9)	88 (20.1)	8 (1.8)
Anemia	125 (28.7)	52 (12.0)	114 (26.0)	37 (8.4)
Constipation	125 (28.7)	5 (1.1)	127 (29.0)	1 (0.2)
Fatigue	112 (25.7)	4 (0.9)	116 (26.5)	11 (2.5)
Alopecia	106 (24.4)	0	105 (24.0)	1 (0.2)
Decreased appetite	71 (16.3)	5 (1.1)	62 (14.2)	3 (0.7)
Pyrexia	68 (15.6)	6 (1.4)	55 (12.6)	0
Vomiting	65 (14.9)	5 (1.1)	63 (14.4)	3 (0.7)
Febrile neutropenia	62 (14.3)	60 (13.8)	35 (8.0)	35 (8.0)
Headache	56 (12.9)	1 (0.2)	57 (13.0)	4 (0.9)
Cough	56 (12.9)	0	53 (12.1)	0
Decreased weight	55 (12.6)	4 (0.9)	52 (11.9)	1 (0.2)
Asthenia	53 (12.2)	7 (1.6)	53 (12.1)	2 (0.5)
Dysgeusia	49 (11.3)	0	57 (13.0)	0

- 4.4% discontinued Pola vs 5.0% for vincristine

Tilly H, et al. N Engl J Med. 2022 Jan 27;386(4):351-363.

POLARIX: R-CHOP vs R-CHP+Pola

Baseline Risk Factors	Total N	Pola-R-CHP (N=440) n	Pola-R-CHP (N=440) 2-year Rate	R-CHOP (N=439) n	R-CHOP (N=439) 2-year Rate	Hazard Ratio	95% Wald CI
Age group							
≤60	271	140	74·1	131	71·9	0·9	(0·6 to 1·5)
>60	608	300	77·9	308	69·5	0·7	(0·5 to 0·9)
Sex							
Male	473	239	75·9	234	65·9	0·7	(0·5 to 0·9)
Female	406	201	77·7	205	75·2	0·9	(0·6 to 1·4)
ECOG PS							
0–1	737	374	78·4	363	71·2	0·8	(0·6 to 1·0)
2	141	66	67·2	75	65·0	0·8	(0·5 to 1·4)
IPI score							
IPI 2	334	167	79·3	167	78·5	1·0	(0·6 to 1·6)
IPI 3–5	545	273	75·2	272	65·1	0·7	(0·5 to 0·9)
Bulky disease							
Absent	494	247	82·7	247	70·7	0·6	(0·4 to 0·8)
Present	385	193	69·0	192	69·7	1·0	(0·7 to 1·5)
Geographic region							
Western Europe, United States, Canada, and Australia	603	302	78.6	301	72.0	0.8	(0·6 to 1·1)
Asia	160	81	74.3	79	65.6	0.6	(0·4 to 1·5)
Rest of world	116	57	70.8	59	67.3	0.9	(0·6 to 1·5)
Ann Arbor stage							
I–II	99	47	89·1	52	85·5	0·6	(0·2 to 1·8)
III	232	124	80·7	108	73·6	0·8	(0·5 to 1·3)
IV	548	269	72·6	279	66·1	0·8	(0·6 to 1·1)
Baseline LDH							
≤ULN	300	146	78·9	154	75·6	0·8	(0·5 to 1·3)
>ULN	575	291	75·4	284	67·2	0·7	(0·5 to 1·0)
No. of extranodal sites							
0–1	453	227	80·2	226	74·5	0·8	(0·5 to 1·1)
≥2	426	213	73·0	213	65·8	0·7	(0·5 to 1·0)
Cell-of-origin							
GCB	352	184	75·1	168	76·9	1·0	(0·7 to 1·5)
ABC	221	102	83·9	119	58·8	0·4	(0·2 to 0·6)
Unclassified	95	44	73·0	51	86·2	1·9	(0·8 to 4·5)
Unknown	211	110	73·8	101	64·3	0·7	(0·4 to 1·2)
Double expressor by IHC							
DEL	290	139	75·5	151	63·1	0·6	(0·4 to 1·0)
Non DEL	438	223	77·7	215	75·7	0·9	(0·6 to 1·3)
Unknown	151	78	76·0	73	69·8	0·8	(0·4 to 1·5)
Double- or triple-hit lymphoma							
Yes	45	26	69·0	19	88·9	3·8	(0·8 to 17·6)
No	620	305	76·8	315	70·3	0·7	(0·5 to 1·0)
Unknown	214	109	78·5	105	66·4	0·6	(0·4 to 1·1)



Tilly H, et al. N Engl J Med. 2022 Jan 27;386(4):351-363.

Double Hit/Double Expressor DLBCL

- DH: DA-EPOCH-R vs DA-EPOCH-R + Venetoclax → trial closed due to toxicity
- DE: R-CHOP vs R-CHOP + Venetoclax → ?

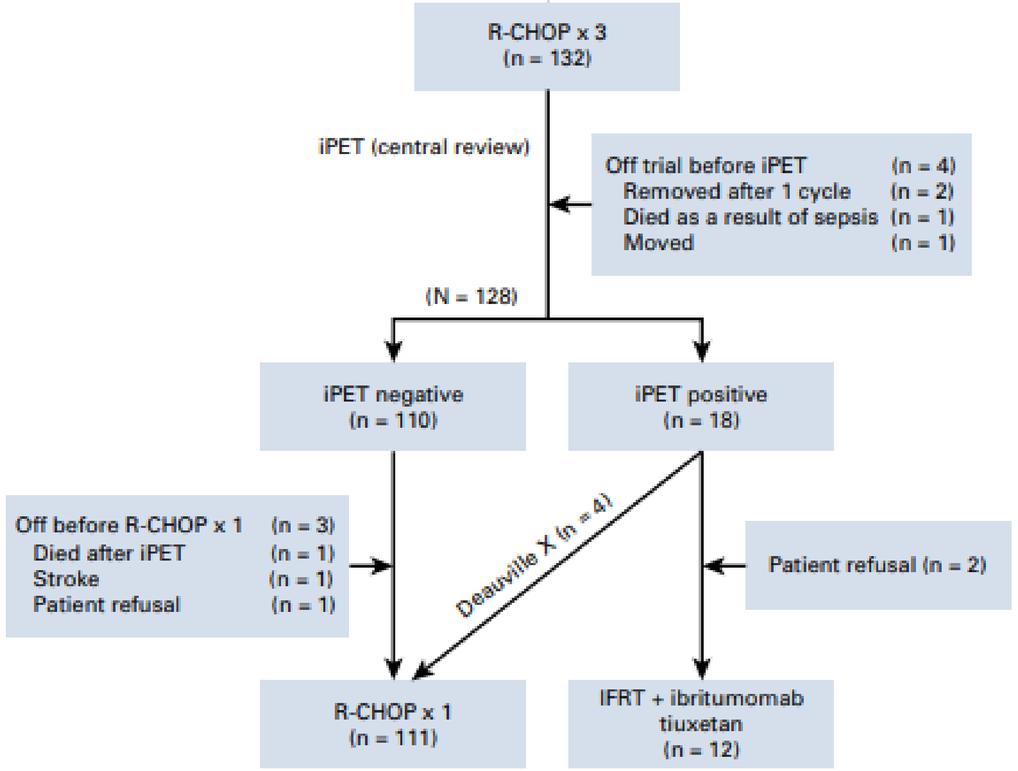
Limited Stage DLBCL (SWOG 1001)

Inclusion criteria

- Stage I/II
- Non-bulky (< 10 cm)

Results

- 110 (89%) were iPET negative received total of 4 cycles of R-CHOP
- With median F/U of 4.5 years the 5 year PFS/OS was 88% and 91% in the iPET negative group



Persky DO, et al. J Clin Oncol. 2020 Sep 10;38(26):3003-3011.

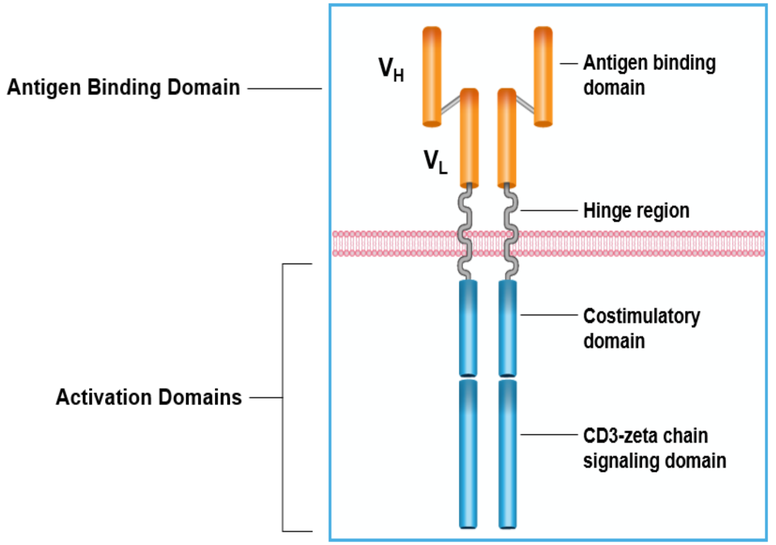
Relapsed DLBCL

Therapy MOA (Approval)	Approved line of therapy
R-Chemo (ie R-Gem/Ox)	≥ 1
Salvage chemo (ie R-ICE) + Auto SCT	≥ 1
Axi-cel [Yescarta], CD19 CAR T	≥ 2 > 1*
Tisa-cel [Kymriah], CD19 CAR T	≥ 2
Liso-cel [Breyanzi] CD19 CAR T	≥ 2 > 1**
Tafasitamab [Monjuvi] CD19 MAB + Lenalidomide	≥ 1
Loncastuximab Tesirine [Zynlonta], CD19 ADC	≥ 2

*In patients relapsing < 12 months from completion of FT therapy

** In patients relapsing < 12 months from completion of FT therapy or in patients not a candidate for auto-SCT

Chimeric Antigen Receptors



scFv
Single-chain variable fragment (scFv) bypasses MHC antigen presentation, allowing direct activation of T cell by cancer cell antigens

Hinge region
Essential for optimal antigen binding

Costimulatory Domain: CD28 or 4-1BB
Enhances proliferation, cytotoxicity and persistence of CAR T cells

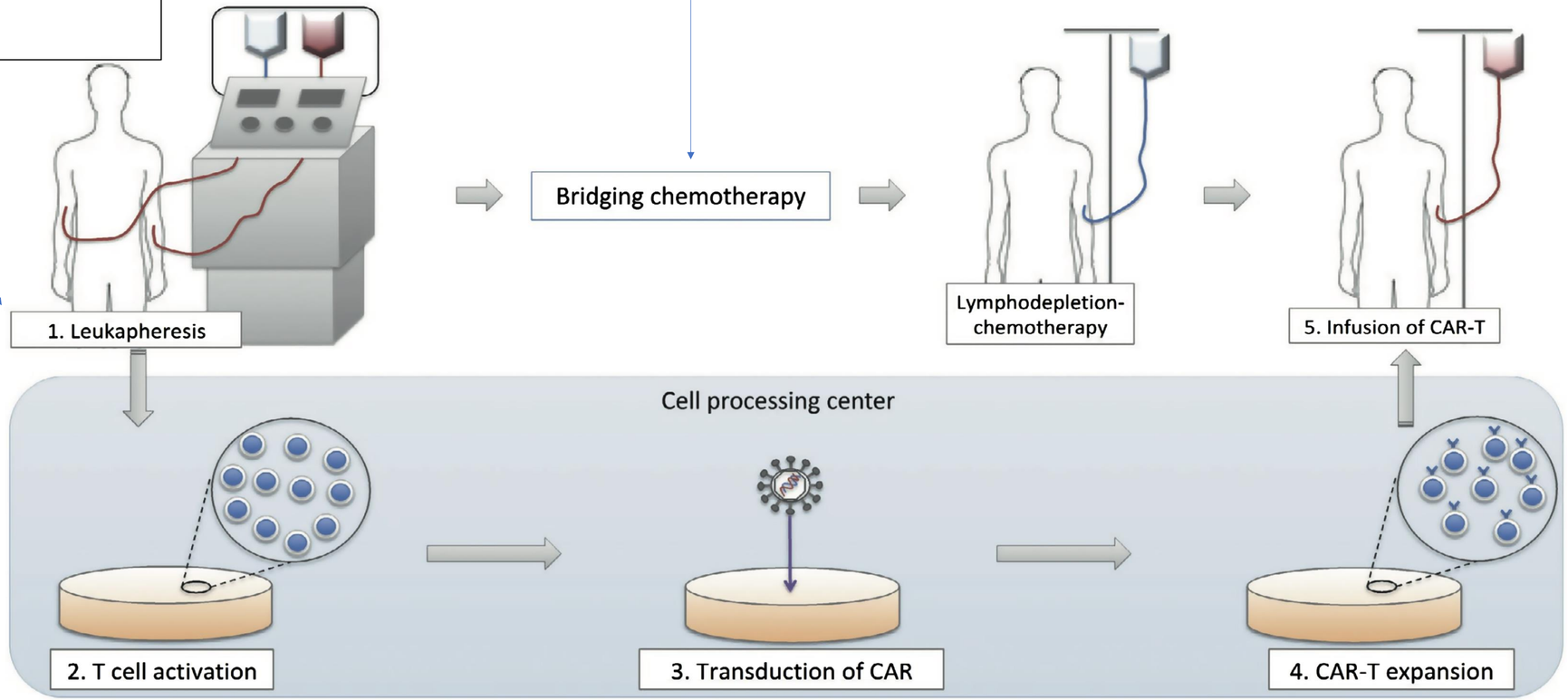
Signaling Domain: CD3ζ chain
Proliferation and activation of CAR T cells CAR T-cell-mediated killing of tumor cells

Zhang H, et al. *J Immunol*. 2007;179(7):4910-4918

Pre-CAR-T Management and Logistics

1. ALC
2. Duration from last therapy (steroids, chemo, RT, small mol inhibitors)
3. Insurance approval

1. Bridging vs no bridging
- Tumor Burden
2. Chemo vs radiation
- Tumor burden

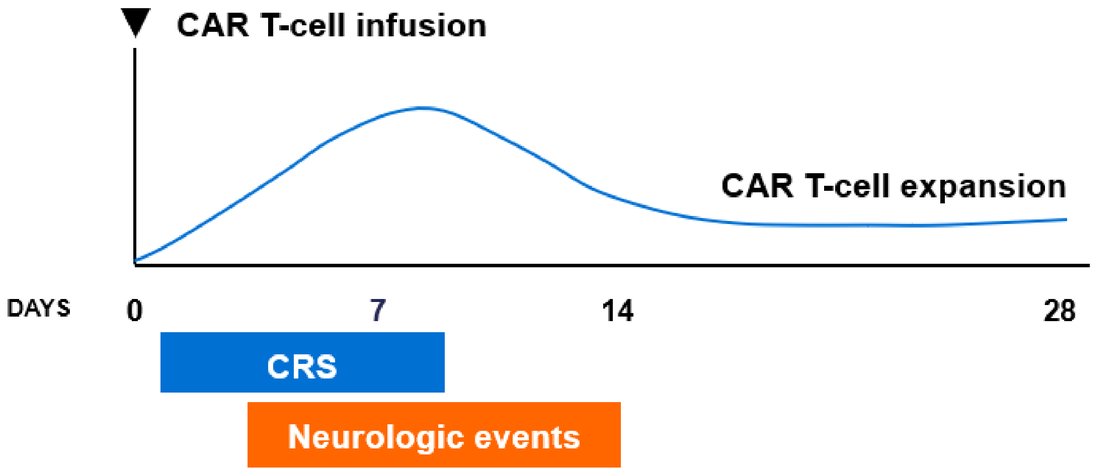


Makita S, et al. Cancer Sci. 2017 Jun;108(6):1109-1118. \

Post-CAR-T Toxicity

- **Cytokine release syndrome**
- **Immune effector cell-associated neurotoxicity syndrome (ICANS)**
- **Cytopenias**
- **Infections**
- MAS or HLH (rare)
- Coagulopathy (rare)
- Tumor Lysis Syndrome (rare)
- Infusion reaction (rare)

Post-CAR-T Toxicity



	Axi-cel	Tisa-cel	Liso-cel
CD19 scFv	FMC63	FMC63	FMC63
Signal 2	CD28	41BB	41BB
Signal 1	CD3ξ	CD3ξ	CD3ξ
CRS: Any/Gr3+ (%)	93/13	57/23	42/2
Neuro tox: Any/Gr3+ (%)	64/28	20/11	30/10

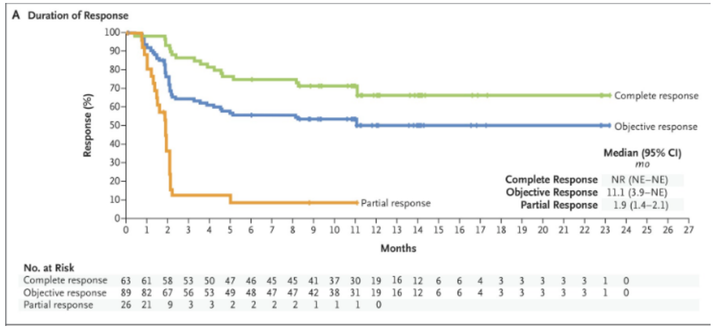
- CRS: fever → hypotension/hypoxemia
- ICANS: headaches, confusion, aphasia, seizures, cerebral edema

Morris EC, et al. Cytokine release syndrome and associated neurotoxicity in cancer immunotherapy. Nat Rev Immunol. 2021
Locke et al. *Mol Ther*. 2015.
Peter Borchmann et al. Stephen Schuster EHA 2018;
Neelapu SS, et al. NEJM, 2018
Abramson JS, Lancet Oncol, 2020

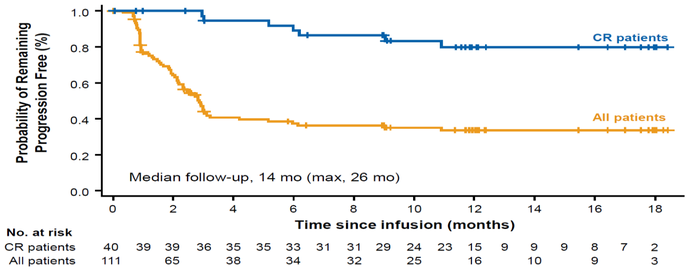
CD19 CAR-T Efficacy in DLBCL as ≥ 3rd Line

	Axi-cel	Tisa-cel	Liso-cel
CD19 scFv	FMC63	FMC63	FMC63
Signal 2	CD28	41BB	41BB
Signal 1	CD3ξ	CD3ξ	CD3ξ
Pivotal trial	ZUMA-1	Juliet	Transform
Most mature follow up (m)	63.1	40.3	24
Median duration of response (m)	11.1	NE	23.1
ORR/CR (%)	83/58	52/39	73/53
Median PFS (m)	5.9	2.9	6.8
PFS, 24 m (%)	36	33*	40.6
Median OS (m)	25.8	11.1	27.3

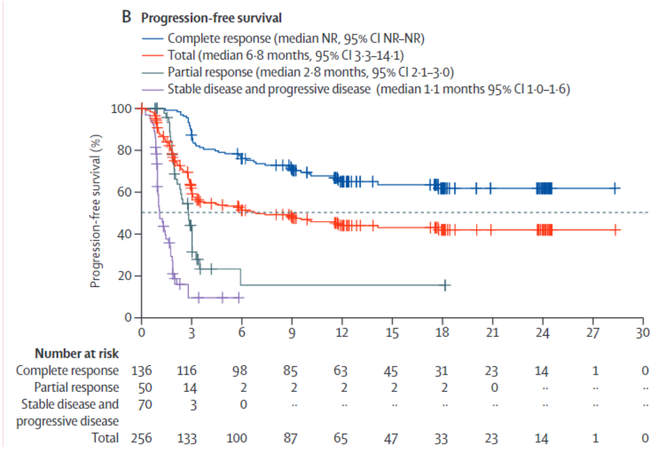
ZUMA-1: Axi-cel



JULIET: Tisa-cel



TRANSCEND: Liso-cel



**SCHOLAR-1: DLBCL patients refractory to previous therapy have ORR of 26%, CR rate of 7%, and an overall survival (OS) of 6.3 months

Crump M, et al. Blood. 2017 Oct 19;130(16):1800-1808.
Peter Borchmann et al. Stephen Schuster EHA 2018
Neelapu SS, et al. NEJM, 2018
Abramson JS, Lancet Oncol, 2020

CD19 CAR-T as 2nd line therapy vs Salvage Therapy and Auto-SCT

(in a high risk population: relapsing < 12 months from completion of frontline therapy)

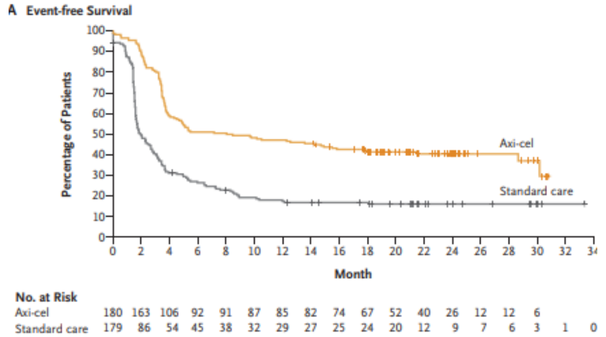
	ZUMA-7	Belinda	Transform
Histologies included	DLBCL NOS,* including transformed from FL, HGBCL with or without MYC and BCL2/6, T/H-RLBCL, Primary cutaneous DLBCL - leg type	DLBCL NOS, including transformed from indolent NHL, HGBCL with or without MYC and BCL2/6, T/H-RLBCL, Primary cutaneous DLBCL - leg type FL grade 3B, PMBCL, Intravascular LBCL, ALK + LBCL, HHV8 + LBCL	DLBCL NOS, including transformed from indolent NHL, HGBCL with MYC and BCL2/6, T/H-RLBCL, FL grade 3B, PMBCL
Product	Axi-cel, CD28/CD3zeta 2×10^6 cells/kg	Tisa-cel, 4 – 1BB/CD3zeta 0.6-6 $\times 10^8$ cells	Liso-cel, 4 – 1BB/CD3zeta 1×10^8 cells
LD chemotherapy	• Fludarabine 30 mg/m^2 × 3 d • Cyclophosphamide 500 mg/m^2 × 3 d	• Fludarabine 25 mg/m^2 × 3 d and • Cyclophosphamide 250 mg/m^2 × 3d OR • Bendamustine 90 mg/m^2 × 2 d	• Fludarabine 30 mg/m^2 × 3 d • Cyclophosphamide 300 mg/m^2 × 3 d
Bridging therapy	• Dexamethasone ≤40 mg for ≤4 d	• R-ICE • R-GDP • R-DHAP • R-GemOx	• R-ICE • R-GDP • R-DHAP
EFS definition	Time from randomization to: • PD • Death • <PR at day 150 assessment • Start of new lymphoma therapy	Time from randomization to: • PD • Death • <PR at/after week 12	Time from randomization to: • PD • Death • ≤PR by week 9 • Start of new lymphoma therapy

Westin J, Sehn LH. Blood. 2022 May 5;139(18):2737-2746.

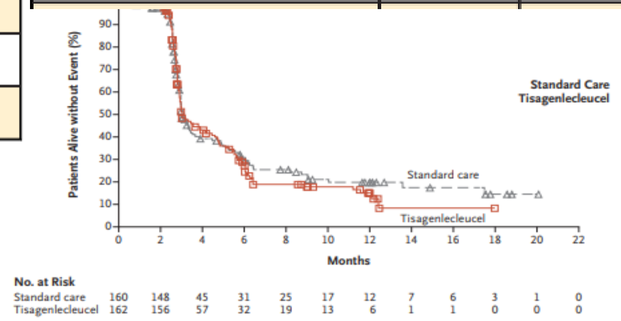
CD19 CAR-T as 2nd line therapy vs Salvage Therapy and Auto-SCT

	ZUMA-7		Belinda		Transform	
	Axi-Cel	SOC	Tisa-Cel	SOC	Liso-Cel	SOC
Received intended CAR T cell (%)	94	—	96	—	97.8	—
Median time to CAR T-cell infusion in days, (interquartile range* or range†)	29 (27-34)*	—	52 (31-135)†	—	NR	—
Received intended ASCT (%)	—	36	—	32.5	—	45.6
Follow up, median in months	24.9		10		6.2	
ORR/CR rate (%)	83/65	50/32	46/28	43 /28	86/66	48/39
EFS, median in months	8.3	2	3	3	10.1	2.3
EFS, % (timepoint in months)	41 (24 mo)	16 (24 mo)	NR	NR	63 (6 mo)	33 (6 mo)
EFS HR (95% CI)	0.4 (0.31-0.51)		1.07 (0.82-1.4)		0.35 (0.23-0.53)	
OS, median in months	NE	25.7	16.9	15.3	NE	16.4
OS HR (95% CI)	0.708 (0.515-0.972)‡		NR		0.51 (0.26-1.004)	

ZUMA-7: Axi-cel



	ZUMA-7		Belinda		Transform	
	Axi-cel	SOC	Tisa-cel	SOC	Liso-cel	SOC
CRS, any grade (%)	92	—	61	—	49	—
CRS, grade ≥3 (%)	6	—	5	—	1	—
Neurologic toxicity, any grade (%)	60	—	10	—	12	—
Neurologic toxicity, grade ≥3 (%)	21	—	2	—	4	—
Tocilizumab use (%)	65	—	32	—	24	—
Corticosteroid usage for toxicity management (%)	24	—	10	—	17	—



Westin J, Sehn LH. Blood. 2022 May 5;139(18):2737-2746.
Locke FL, et al. NEJM, 2021
Kamdar M, et al. ASH abstract #91
Bishop MR, et al. NEJM, 2021

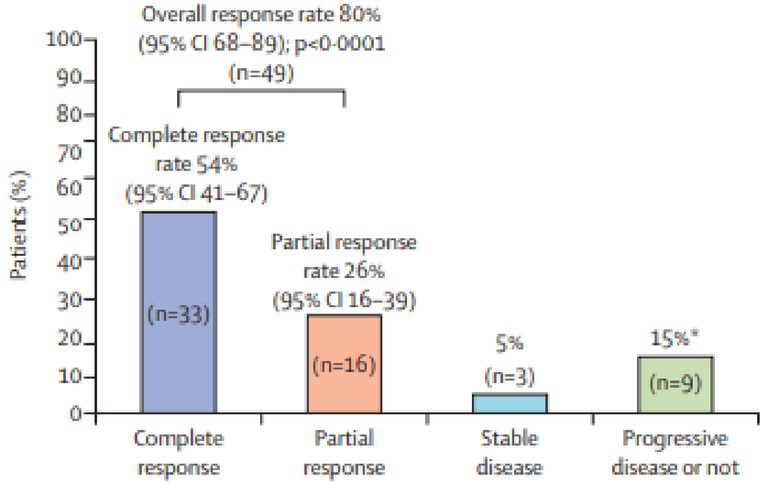
PILOT Study: CD19 CAR-T as 2nd line therapy in patients ineligible for Auto-SCT

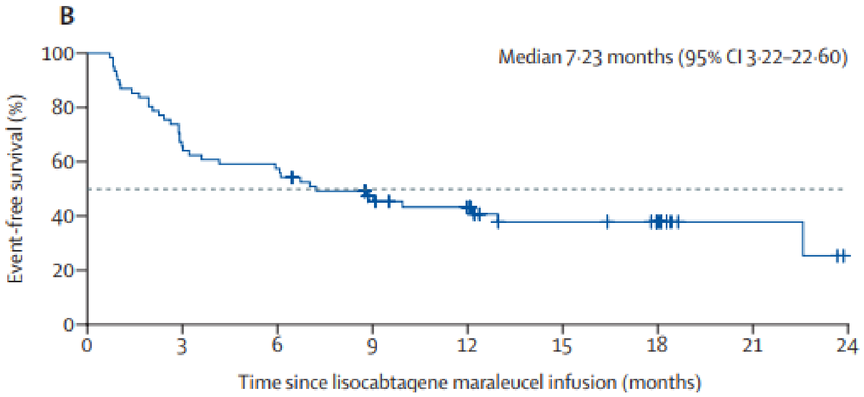
Inclusion criteria

- Relapsed after anthracycline/CD20 MoAb containing regimen
- ≥ 1 of the following
  - ≥ 70
  - ECOG 2
  - DLCO ≤ 60%
  - LVEF < 50%
  - CrCl < 60 ml/min
  - ALT/AST > 2 x ULN

CRS:
- Any/Grade 3+: 38%/2%
- Toci and/or steroids: 26%

Neurological events
- Any/Grade 3+: 31%/5%
- Steroids: 13%





Median PFS of CR patients: 22.6 months (95% CI 12.98 – NR)

Sehgal A, et al. Lancet Oncol. 2022 Aug;23(8):1066-1077..

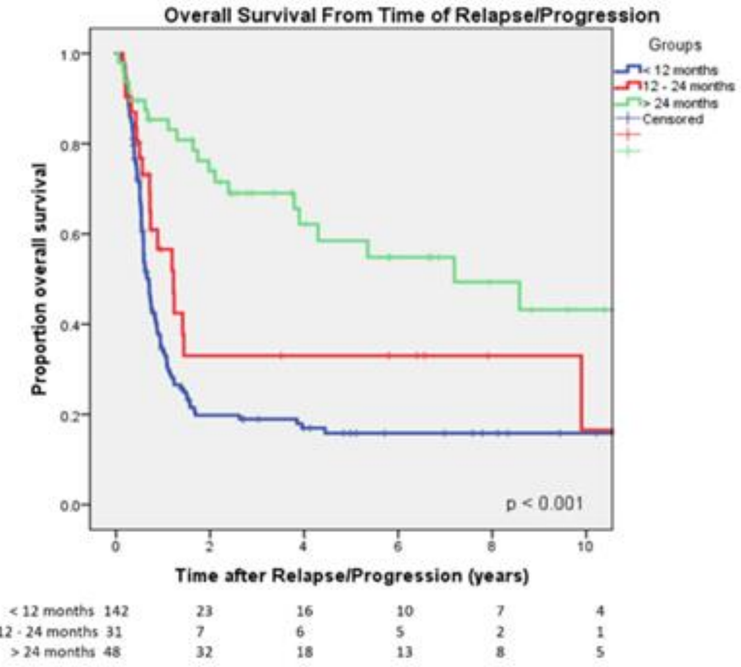
Current FDA Indications for CD19 CAR-T in DLBCL

1. Axi-cel/Yescarta
   - > 1 line of therapy (if refractory or relapsed within 1 year of completion of frontline chemotherapy)
   - ≥ 2 lines of therapy

2. Tisa-cel/Kymriah
   - ≥ 2 lines of therapy

3. Liso-cel/Breyanzi
   - > 1 line of therapy (if refractory or relapsed within 1 year of completion of frontline chemotherapy OR if relapsed > 1 year after frontline therapy but not a candidate for autologous stem cell transplant)
   - ≥ 2 lines of therapy

DLBCL patients relapsing > 12 months from FT therapy



Ngu HS, Hilton LK, Rodrigo JA, et al. Blood. 2021;138(suppl 1). Abstract 2499.

Treatment Outcomes post CD19 CAR-T Relapse

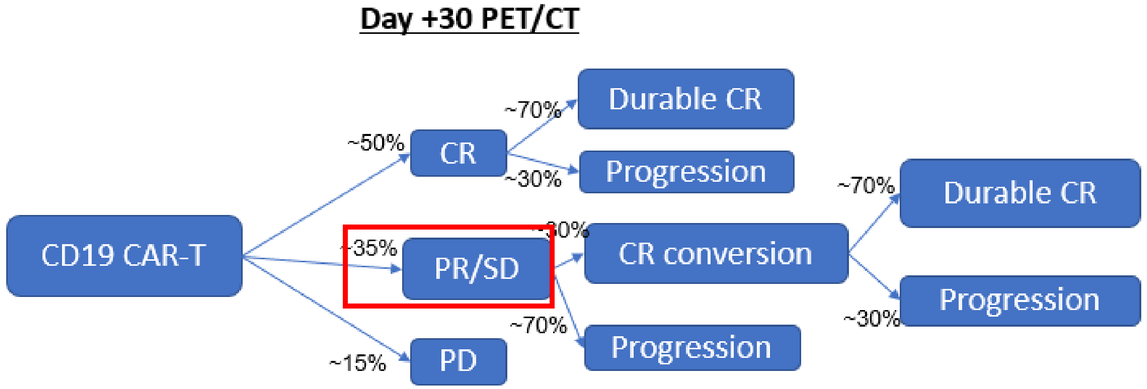
Mechanism of Relapse

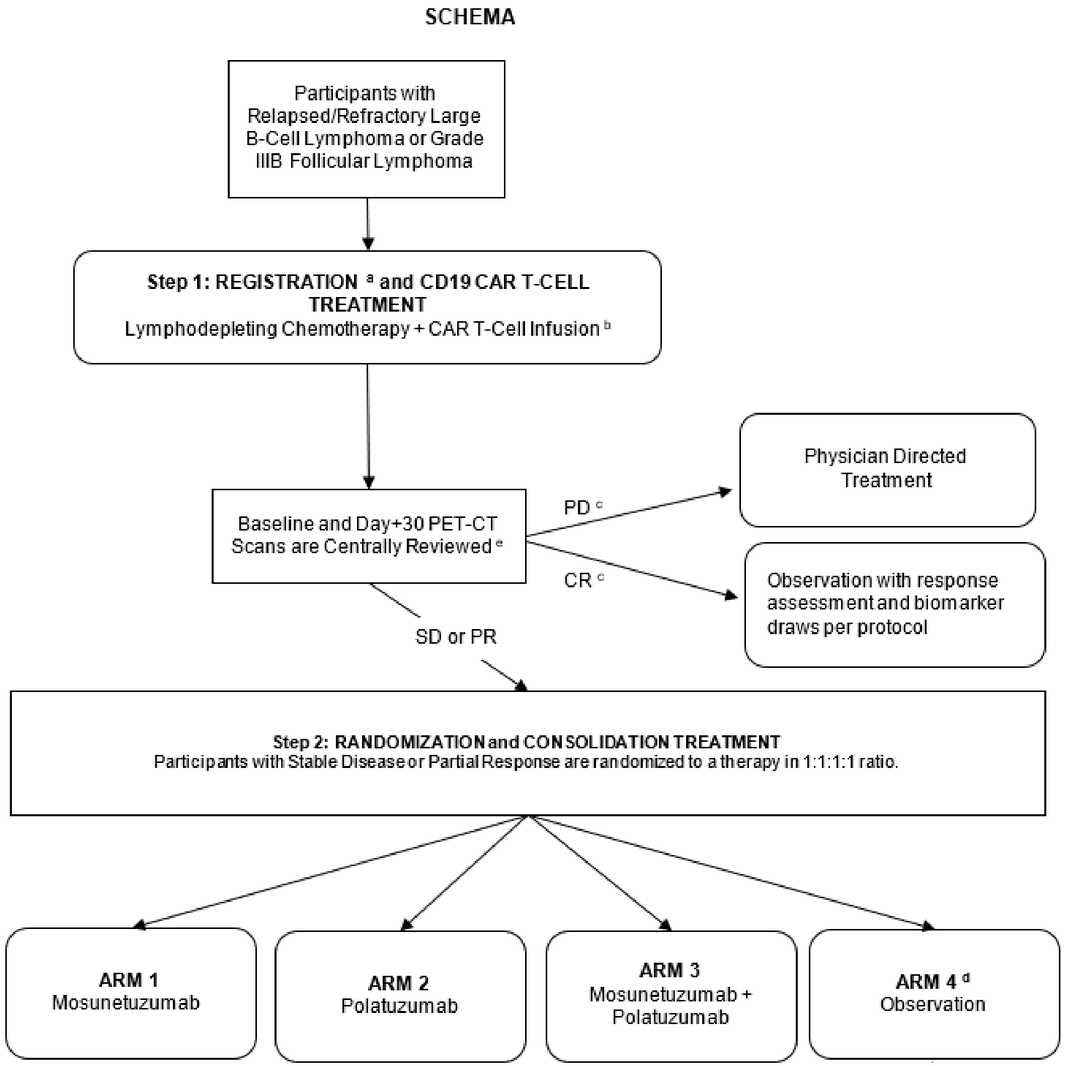
- CD19 Loss (Neelapu SS, et al. Blood. 2018:578; Oak J, et al. Blood. 2018)
- Upregulation of immune checkpoint molecules
- CAR-T 'exhaustion' (Locke F, et al. Blood, 2020)

Therapy	CR	ORR	Median PFS (95% CI), d	Median OS (95% CI), d
Checkpoint inhibitor based (n = 28*)	18%	46%	88 (35-282)	331 (168-477)
Chemotherapy (n = 17)	12%	18%	51 (21-64)	104 (51-231)
Lenalidomide based (n = 27)	19%	19%	48 (33-84)	139 (45-NE)
Radiation (n = 10)	20%	30%	58 (20-149)	220 (20-NE)

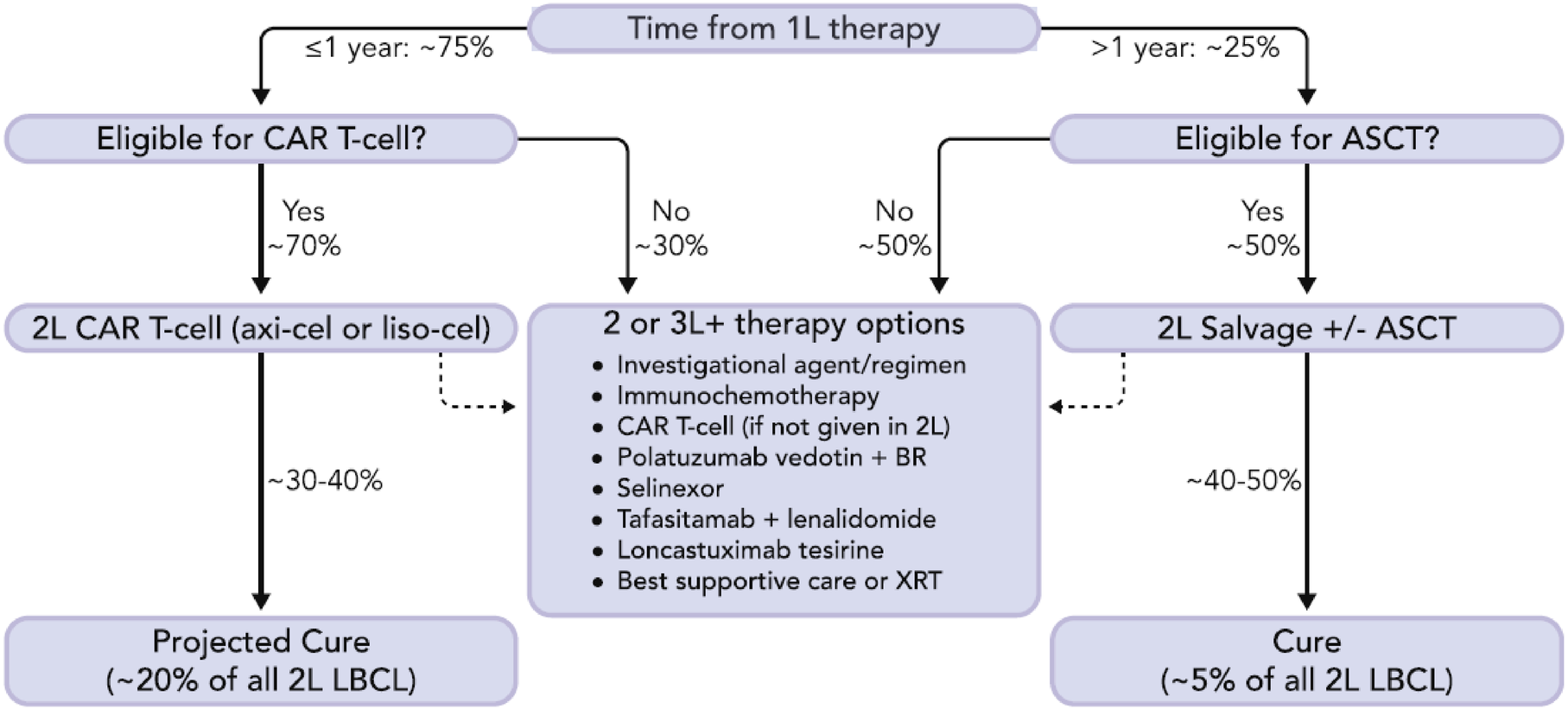
Spiegel JY, et al.. Blood. 2021 Apr 1;137(13):1832-1835.

Preventing Relapse post CD19 CAR-T in High Risk LBCL Population





Algorithm for 2nd Line Therapy in LBCL



Westin J, Sehn LH. Blood. 2022 May 5;139(18):2737-2746.

On the Horizon..

- Frontline trials based on tumor biology
- Frontline CAR-T (in High risk populations)
- BITE (CD3-CD20): Frontline and relapse
  - **Glofitamab in patients with relapsed/refractory (R/R) diffuse large B-cell lymphoma (DLBCL) and ≥ 2 prior therapies: Pivotal phase II expansion results.**
  - **First-line treatment (Tx) with subcutaneous (SC) epcoritamab (epco) + R-CHOP in patients (pts) with high-risk diffuse large B-cell lymphoma (DLBCL): Phase 1/2 data update.**
  - **Mosunetuzumab plus polatuzumab vedotin has promising efficacy and favorable safety profile in patients with relapsed/refractory aggressive B-cell NHL**
- CD19 targeted therapies after CD19 CAR-T relapse
- MRD adaptive therapy
- CNS Prophylaxis

Clinical Trials in LBCL near you

MUSC/HCC

Frontline

- **R-mini-CHOP +/- Oral Azacitadine in patients ≥ 75 (Phase II/III)**
- **R-CHOP + Zanubrutintib (Phase 1B)****

Relapsed

- **Loncastuximab Tesirine + Polatuzumab Vedotin (Phase 1B)**
- **Auto-SCT +/- Ibrutinib maintenance in ABC subtype (Phase III)**
- **GEN3009 (DuoHexaBody®-CD37) (Phase I)**
- **Epcortimab (CD3-CD20 BITE) – (Phase II)****
- **S2114: Maintenance therapy with Mosun, Pola, or Mosun+Pola vs observation in patients with SD/PR at day +30 post CAR-T (Phase II)****
- **Metabolically Fit CD19 CAR-T with CD34 selection (Phase 1B)****
  - **DLBCL/PMBCL, FL, MCL (FDA approved subtypes)**
  - **MZL, LPL/WM, CLL/SLL, Burkitt, etc (Non-FDA approved subtypes)****

Prisma/Greenville

Frontline

- **R-CHOP +/- Tafasitamab + Lendalidomide (Phase III)**

Relapsed

- **Auto-SCT +/- Ibrutinib maintenance in ABC subtype (Phase III)**
- **Epcortimab in outpatient setting (Phase II)****

** Trials to be open for enrollment in the next 1-2 months